New Series Volume 1 Number 4

The American Journal of

DIGESTIVE DISEASES

April 1956

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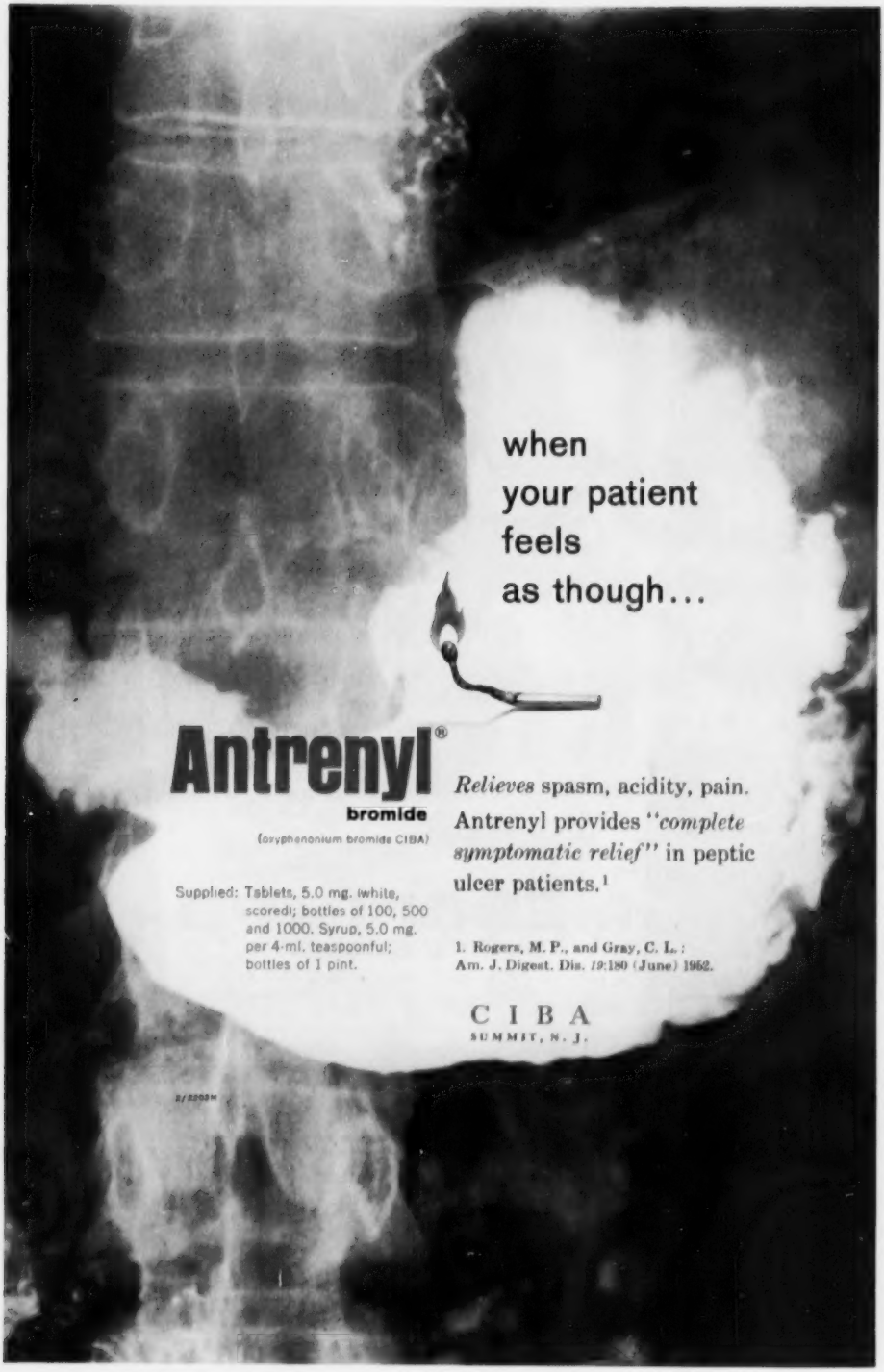

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The American Journal of

DIGESTIVE DISEASES

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The American Journal of

DIGESTIVE DISEASES

THE AMERICAN JOURNAL OF DIGESTIVE DISEASES is a clinical journal edited primarily for physicians and surgeons engaged in active practice and concerned directly with diagnosis and care of patients. It is devoted to prompt publication and dissemination of soundly based investigation and clinical study in the field of Gastroenterology broadly defined. The Journal includes within its scope the practical aspects of diseases of the digestive system, including nutritional and metabolic disturbances and diseases of the liver.

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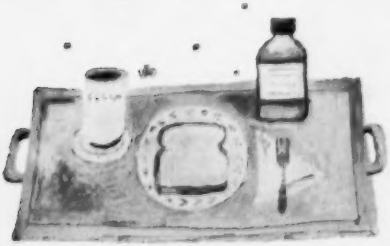

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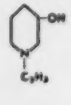

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Esophageal Varices Caused by Metastasis of Carcinoma to the Liver

ARCHIBALD L. RUPRECHT, M.D., and
THOMAS D. KINNEY, M.D.

VARICES of the esophagus are well-known sequelae of obstruction to the flow of portal blood, but it is not widely recognized that they may occur when the obstructive lesion is due to metastatic carcinoma in the liver. Reports of a few such cases are to be found in the literature, but there has been no attempt to emphasize this basis for melena and hematemesis. Generally, when patients with disseminated carcinoma show evidence of chronic portal obstruction, constriction of the portal vein by tumor is assumed, and although this is a common finding many of these patients have neoplastic masses in the liver as well. Attention has not been drawn to the role of hepatic metastases in the production of a portal block. For this reason, 4 cases are reported and 6 cases from the literature are discussed in which esophageal varices were the result solely of metastases to the liver. The present material was encountered during a short enough period of time to indicate that this is not a rare occurrence. Almost any carcinoma may produce this picture, but tumors of abdominal organs are most apt to invade the liver massively and predominate in such a group of cases. If bleeding from the esophagus occurs in the absence of physical signs of portal obstruction, neoplastic stenosis of the portal vein will not seem likely, and diagnosis may be obscured unless hepatic metastases are borne in mind as a basis for varices. In 2 of the 4 patients who have recently come to our attention, the episodes of esophageal bleeding included 2 fatal hemorrhages.

CASE REPORTS

Case 1

A 56-year-old woman (Cleveland State Hospital 29139) complained for 2 months of increasingly severe attacks of nausea, vomiting, and abdominal distention. Cecostomy was done in December, 1944, and the following month an adenocarcinoma of the sigmoid colon was removed and

From the Department of Pathology, Western Reserve University School of Medicine at City Hospital, Cleveland, Ohio.

end-to-end anastomosis of the bowel performed. Metastases were not noted at operation. The cecal fistula was permitted to remain although the abdominal symptoms were entirely relieved. A year later the patient had an emesis of bright red blood, and by the end of 2 years she had become emaciated and the liver edge was nodular and palpable 4 fingerbreadths below the right costal margin. In September, 1947, 2 years and 9 months after resection, the patient had another hematemesis, larger than the first, and thereafter tarry material oozed intermittently from the cecal fistula. There was progressive enlargement of the abdomen due to ascites. During the last few days of life the patient became slightly icteric and vomited altered blood repeatedly. In December, 1947, 3 years after removal of the tumor and 2 years after the initial bloody vomitus, she died following massive hematemesis.

Autopsy Findings (CCH 17287)

THE STOMACH was filled with partially clotted blood. There were many dilated varices on each side of the esophagogastric junction (Fig. 1). There was a small ulcerated area in the mucosa of the lower esophagus through which a probe could be passed into a large varix.

THE LIVER weighed 5325 Gm. The greater part of the right lobe and three fourths of the left were replaced by confluent masses of metastatic carcinoma (Fig. 2). For a distance of 4 cm. from the inferior vena cava the hepatic veins were unaltered, but deeper in the liver they were compressed by tumor tissue which invaded and occluded some of their primary branches. The right and left portal veins were compressed similarly so

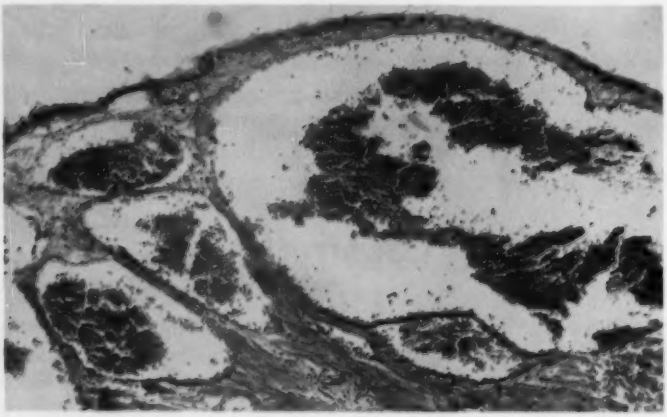

Fig. 1. **Case 1. Section of lower esophagus from patient with adenocarcinoma of sigmoid. (H & E, × 168).**

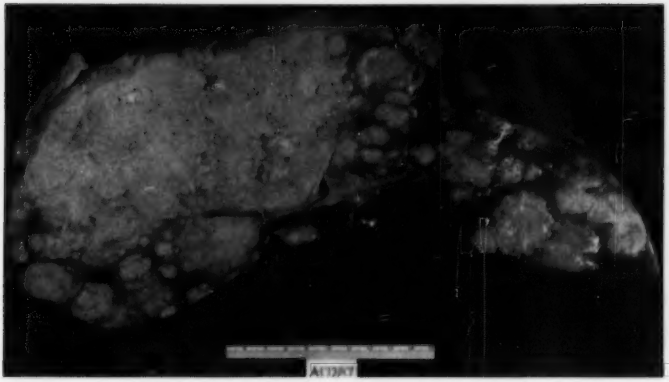

Fig. 2. **Case 1. Cross-section of liver.**

that only a short segment of each was normally patent. Further, many of the major radicles of these veins were filled with casts of neoplastic tissue, and in microscopic sections numerous small veins were seen to be obstructed by thrombi containing tumor cells. The tumor was a well-differentiated adenocarcinoma, histologically similar to the tumor removed from the sigmoid. Away from metastases the normal architecture of hepatic parenchyma was preserved. Some large bile ducts within the liver were compressed by tumor nodules, but the extrahepatic biliary tract was normal. The portal vein proper was free of thrombi and slightly dilated.

THE SPLEEN was hyperemic and weighed 230 Gm. No residual tumor was found in the sigmoid colon.

THE PERITONEAL CAVITY contained 8 L. of clear yellow fluid with a specific gravity of 1.016. There were tumor nodules in the omentum and on the serous surfaces of the abdominal viscera. Metastases were also present in: an ovary and adrenal gland; both lungs; and in mediastinal, periportal, mesenteric and retroperitoneal lymph nodes.

Case 2

A 57-year-old molder (Cleveland City Hospital 277018), known to have had quiescent pulmonary tuberculosilicosis for many years, was hospitalized in December, 1947, for investigation of hemoptyses and weight loss during the preceding 10 months. The significant physical findings were signs of consolidation in the upper lobe of the right lung and hepatic enlargement to 4 fingerbreadths below the right costal margin. On bronchoscopic examination a tumor mass was seen to partially occlude the orifice of the bronchus in the right upper lobe. The patient's condition deterio-

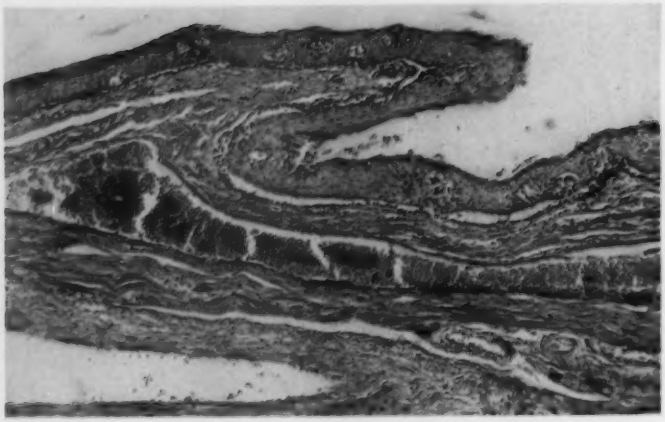

Fig. 3. **Case 2. Section of lower esophagus from patient with bronchogenic carcinoma and hepatic metastases. (H & E, × 168).**

rated rapidly and he died 6 weeks after admission. He did not develop icterus, and at no time was there evidence of bleeding from the upper digestive tract.

Autopsy Findings (CCH 17396)

THE BRONCHIAL TUMOR was an undifferentiated carcinoma. Silicotic nodules were distributed throughout the lungs and there was tuberculosilicosis in the right upper lobe.

THE ESOPHAGEAL VEINS, particularly near the cardia, were markedly dilated and covered by a thin layer of mucosa (Fig. 3).

THE LIVER was greatly enlarged and weighed 4200 Gm. Tumor metastases measuring up to 4.5 cm. in diameter were evenly distributed throughout (Fig. 4). In microscopic sections the hepatic lobules were of normal appearance except where compressed or partially replaced by carcinomatous tissue. Within the metastatic masses and about their periphery tumor thrombi were often noted in portal venules and to a lesser extent within central veins; they were not seen in branches of hepatic arteries. The tumor was wholly undifferentiated, and many neoplastic cells contained mitotic figures. The portal trunk, its large branches in the liver, and the major hepatic veins were all widely patent.

THE SPLEEN weighed 150 Gm. There was no excess peritoneal fluid. The lumen of the superior vena cava was not narrowed.

TUMOR METASTASES were found in the inguinal, retroperitoneal, and mesenteric lymph nodes; the stomach; small bowel; left kidney; adrenal glands; and ribs and vertebrae.

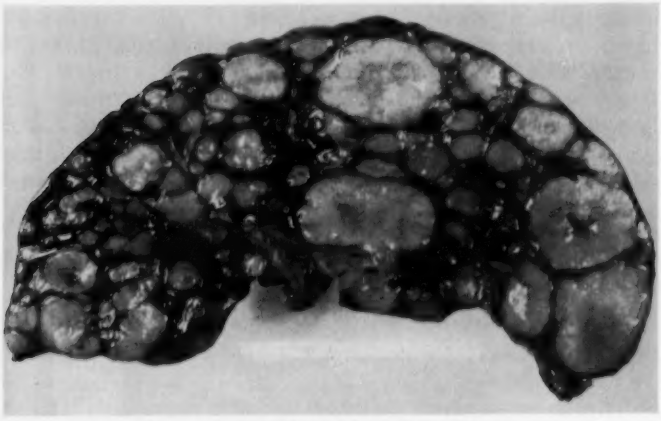

Fig. 4. Case 2. Coronal section of liver.

Case 3

A 65-year-old woman (Cleveland City Hospital 290499) entered the hospital in September, 1947, complaining of weakness, loss of appetite, and a progressive swelling of the abdomen for 2 months. She had not vomited nor had she noted a change in stool color.

On physical examination ascites and marked pitting edema of the lower half of the body were apparent. Following abdominal paracentesis the lower margin of the liver was felt 6 cm. below the right costal border. Separate from the liver was an irregular epigastric mass. Laboratory data suggested that the peripheral edema was caused by obstruction, there being no anemia, hypoproteinemia, or evidence of cardiac or renal disease. A few days before death the patient became slightly icteric. She died following a massive hematemesis.

***Autopsy Findings* (*CCH 17186*)**

THE TRANSVERSE COLON showed a well differentiated adenocarcinoma.

ESOPHAGEAL VARICES were present, and 2 of these had ruptured through the mucosa.

THE LIVER weighed 4275 Gm. and contained many deposits of metastatic tumor; these were close together and in the right lobe formed a confluent mass measuring 14 cm. in diameter. The portal vein proper and major hepatic veins were normally patent, but in the right hepatic lobe most large branches of the two venous systems were either compressed or invaded by tumor. On the left side the same process was less fully developed, but a fresh thrombus largely filled the left portal vein and some of its branches. In microscopic sections many small veins were plugged with

neoplastic casts. Cirrhosis was not present. Some of the large bile ducts in the liver were compressed between metastases and occluded, but the extrahepatic biliary tract was normal.

THE SPLEEN weighed 150 Gm.

THE PERITONEAL CAVITY contained 3 L. of serosanguineous fluid with a specific gravity of 1.018. The serous surfaces of the abdomen were free of carcinoma, the only other deposits being in the lymph nodes of the transverse mesocolon. There were no other significant findings.

Case 4

A 61-year-old man (Cleveland City Hospital 271609) was hospitalized in April, 1948, because of 6 weeks of intermittent abdominal pain associated with weight loss and jaundice. Melena had not been noted and hematemesis had not occurred.

On physical examination there was moderate icterus and the liver was enlarged to 6 cm. below the right costal margin. An annular filling defect was visualized in the sigmoid colon by barium enema. On the fourth hospital day the patient vomited a large amount of altered blood and after passage of a Miller-Abbott tube for control of increasing abdominal distention such emeses were frequent and copious. On the tenth hospital day abdominal distention was still marked and cecostomy was performed. This gave the patient some relief until his death a few days later.

Autopsy Findings (CCH 17528)

THE SIGMOID COLON showed a well-differentiated mucinous adenocarcinoma.

THE MUCOSAL SURFACE OF THE DISTAL ESOPHAGUS was granular and when the esophagogastric junction was transilluminated, large veins were visible; microscopic sections disclosed ulcerative esophagitis and well-developed varices. The hemorrhoidal veins were also ectatic and a few contained antemortem thrombi.

THE LIVER weighed 3100 Gm. Deposits of metastatic tumor replaced three fourths of the right lobe and at least a third of the left. In areas free of metastases the hepatic architecture was normal. In the right lobe there was confluence of tumor nodules to form a large mass which compressed the right portal vein, the lumen of which was narrowed still further by a partially organized thrombus, and some of the large branches of this vessel contained neoplastic casts. The left portal vein and its main radicles were normally patent. Except for freedom from thrombi, the hepatic venous system was involved to an equal extent. In microscopic sections tumor thrombi were present in venules and lymphatics adjacent to metastases. The portal vein proper was of normal appearance, as were the hepatic venous trunks. Several large bile ducts in the liver were compressed be-

tween tumor masses. The gallbladder and extrahepatic biliary passages were free of abnormalities. The spleen weighed 125 Gm.

THE PERITONEAL CAVITY contained 8 L. of yellow fluid with a specific gravity of 1.010.

TUMOR METASTASES were found in gastroepiploic and retroperitoneal lymph nodes and within the lungs and vertebrae.

DISCUSSION

In these four cases the obstruction to the flow of portal blood was attributed to the extensive metastases to the liver. In none of these instances was there any evidence of cirrhosis nor was there thrombosis or compression of a splenic vein or portal trunk. Three of the primary tumors were adenocarcinoma of the large bowel and the fourth was a bronchogenic carcinoma. The varices were asymptomatic in 1 case; in the others there were multiple episodes of bleeding and 2 of the patients died following massive hematemesis. Most of the hemorrhages occurred during the last few weeks of life but in 1 case the first emesis occurred 1 year after the primary growth was removed from the colon and 2 years before death. Icterus was present in 2 patients at the time their varices bled, but in view of an anatomic basis for hemorrhage, the jaundice was of secondary importance.

Absence of Physical Signs of Portal Obstruction

It is worth emphasizing that in 1 of our cases, esophageal varices were the sole manifestation of portal block and that in another, hematemesis took place many months before the development of ascites. These episodes indicate that in such patients esophageal bleeding occasionally will occur in the absence of physical signs of portal obstruction. At such times, neoplastic constriction of the portal vein will not seem likely and diagnosis may be obscured unless hepatic metastases are borne in mind as a cause of varices.

Frequency of Portal Obstruction Caused by Hepatic Metastases

In compiling causes of esophageal varices from autopsy data, Weinberg encountered 4 cases in which numerous hepatic metastases were responsible for the esophageal shunt.[1] The tumor arose from a different organ in each patient, the primary sites being the stomach, kidney, colon, and adrenal cortex. In a group of 16 patients suffering from pancreatic carcinoma Duff[2] found 2 who had hematemeses due to portal obstruction and in whom neoplastic masses in the liver were the only cause of block. The fact that the 4 cases reported here came to

autopsy during an 8-month period suggests that hepatic metastases are not a rare but only a poorly documented cause of portal obstruction.

Anatomic Processes in Esophageal Shunt

Attributing varices to neoplastic stenosis of the portal vein, however, is contrary to the fact that an esophageal shunt is commonly the result of intrahepatic block.[3-5] When there is obstruction to portal flow the route taken by the blood depends in large measure on whether the liver or portal vein is the site of hindrance; in either case the collaterals developed are those best suited to permit a bypass of the obstruction. If the block is intrahepatic, portal blood seeks systemic veins via well-known routes that include the venous plexuses of the rectum and esophagus. Such vessels allow a bypass of the liver and become conduits for a hepatofugal circulation.

However, when the liver is normal but the portal trunk is occluded, the tendency is for blood to find its way about the block and into hepatic tissue via other veins. For example, the route may be via the splenic vein to the gastric venous bed, blood reaching the liver through venous trunks derived from the veins of the gastrohepatic ligament. Occasionally this so-called hepatopetal shunt is handled by an anomalous vein that bridges the obstruction. Usually not enough collaterals of this sort are developed, since the ability to form them certainly varies, and stenosis of the portal vein will incite a hepatofugal circulation as well. Typically, however, the latter type of shunt results from an intrahepatic block, esophageal varices usually being associated with such a lesion.

Massive Invasion of Liver

Ours and similar cases from the literature indicate that for hepatic metastases to cause ectasia of esophagogastric veins, there must be massive invasion of the liver. The average weight of that organ in our patients was 4200 Gm., the heaviest liver weighing 5325 Gm. or nearly 4 times the normal weight. In the absence of cirrhosis, a diagnosis of metastatic tumor is suggested by focal hepatic enlargement, but in our cases, invasion was so extensive as to produce diffuse increase in size. Massive involvement is denoted also by the presence of icterus in 3 of 4 patients, as jaundice due solely to hepatic metastases is rare unless the neoplastic masses are very numerous. Comparable details

about the 6 cases from the literature are lacking, but widespread hepatic invasion was characteristic.

Site of Original Tumor in Relation to Hepatic Metastasis

The degree of involvement of the liver is the key to the origin of tumors apt to produce esophageal varices by this means. Cancers arising in organs of the portal bed have the highest incidence of hepatic metastases,[7] and it is logical that growths with the best chance of metastasizing to the liver will also be those likely to invade it massively. In three fourths of the collected cases the primary tumor was in the pancreas, stomach, or colon. The opportunity for such growths to invade hepatic tissue is enhanced by their tendency to implant on the peritoneum, thus permitting access to additional branches of the portal venous tree.

Duff[2] drew attention to the special opportunity for massive hepatic invasion enjoyed by tumors of the pancreatic body and tail, the 2 examples in the present series being from his collection of cases. Because the splenic vein extends the length of the distal pancreas and is centrally placed, it is invaded by a high percentage of cancers arising in that location, and because the vein is also large, a tumor of the body or tail can inoculate venous blood over a long time before the growth enlarges sufficiently to induce thrombosis of the vessel. In no other location within the abdomen does this situation exist, save in the relation of portal vein to common bile duct, and cancer of the latter is usually rapidly fatal.

Nature of Obstruction

The nature of venous block in these patients is readily identified on examination of the livers. In 2 of our cases there was a mural thrombus in a major intrahepatic branch of the portal vein, and although clots of this type may precipitate esophageal bleeding, they are secondary to the obstruction resulting from cancerous invasion of the 2 venous beds of the liver. In 3 of our cases neoplastic casts were found in large branches of hepatic and right and left portal veins, and in the fourth patient metastases were small and discrete, and invasion of large intrahepatic veins had not occurred. Microscopic sections from all livers disclosed cancerous thrombi in many venules and focal replacement of capillary-rich parenchyma with less vascular tumor tissue. Other descriptions[2, 6, 8] of livers invaded by secondary cancer include mention

of these changes as well as rupture of veins from expanding neoplastic thrombi.

Progression of Metastatic Venous Disruption

When the ways in which hepatic metastases retard venous flow in the liver are viewed as phases of a single process they form a picture of unrelenting progression: neoplastic emboli to portal venules; intravenous growth of cancer; rupture of veins and replacement of adjacent hepatic tissue; and, as the neoplastic masses enlarge, compression of other venous channels, both portal and hepatic, leading in turn to their thrombosis or invasion by tumor. If cancerous emboli reach the liver via systemic blood and lodge in hepatic arterioles, nearby veins are soon invaded and the sequence of events is the same. With increase in the size of hepatic metastases, larger and larger veins are subjected to this obliterative process, ultimately disrupting both intrahepatic venous beds.

SUMMARY

Four cases have been reported in which esophageal varices followed extensive invasion of the liver by metastatic carcinoma. Portal obstruction in these cases is due to neoplastic invasion of the two intrahepatic venous systems and to compression and thrombosis of their branches.

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Phenmetrazine in the Management of Obesity

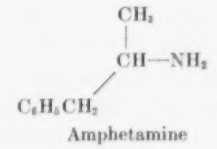
E. PHILIP GELVIN, M.D., THOMAS H. McGAVACK, M.D., and SAMUEL KENIGSBERG, M.D.

PHENMETRAZINE* is a white, odorless, crystalline powder with a slightly bitter taste. In acute-toxicity studies in white mice, its LD_{50} by the oral route is 475 mg./kg., compared to 95 mg./kg. for amphetamine. Unanesthetized dogs receiving a dose of 15 mg./kg. subcutaneously show a degree of excitement similar to the effect of 2.5 mg./kg. of amphetamine.[1]

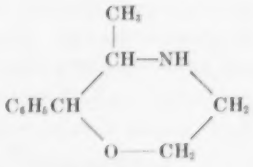
Phenmetrazine has been used clinically in Germany in the management of obesity. Berneike, in a series of 50 obese patients, gave 1 25-mg. tablet twice daily for 10 weeks. All his patients lost weight, the reduction varying from 0.75 to 1.0 kg. (1.75 to 2.2 lb.) per week, with an average of over the entire period of treatment of 0.875 kg. (1.9 lb.) per week.[2] Similar results were reported by Rostalski and König. When phenmetrazine became available in this country, the following study was undertaken to see whether the results of these previous investigators could be duplicated.

From the New York Medical College, Metropolitan Medical Center Research Unit, New York, N. Y.

* Phenmetrazine is one of a new group of chemical compounds with a sympathicomimetic action. In contrast to the amphetamine compounds, the side chain has been replaced by an oxazine ring. Its chemical formula bears the following relationship to that of amphetamine:



Amphetamine



Phenmetrazine

MATERIALS AND METHODS

The double blind technic was employed. The tablets were labeled Compound A and Compound B and were identical in appearance. It was not until the study was completed and the data were tabulated that the investigators were told which was the active medication and which the placebo.* The tablets of the active medication contained 25 mg. of phenmetrazine.

All subjects were patients attending the obesity clinic of the Welfare Island Dispensary, New York City. No patient with edema was included in this study. All except 1 of the patients were women. Their average age was 47 years, average weight at the time they entered the study 202 pounds, and average height 62 inches.

At the first interview a history was taken and a physical examination was done. The importance of strict adherence to diet was emphasized, and the diet described to each patient individually by the dietitian. The daily allowance of 1000 calories was divided among 75 Gm. of protein, 100 Gm. of carbohydrate, and 40 Gm. of fat. The diet was considered adequate in mineral and vitamin content and therefore no supplements were prescribed. All patients received the same diet, which was kept constant during the entire period of observation.

Each subject was given either Compound A or B with instructions to take 1 tablet 3 times a day, 20 minutes before each meal. Patients were alternated as to which medication was prescribed initially. Revisits were every second week.

It was planned that each patient would be observed for a period of about six weeks while taking each of the medications, thus serving as her own control. Some of the patients were lost from the study before this could be accomplished. Forty-five subjects were observed while taking each of the medications. Of these, 22 received Compound A as the initial medication. Several of this group of 45 subjects were observed for longer periods of time, thus affording observation during more than one course of one or both medications. Seventeen patients were followed through two courses of Compound A, and 1 through three courses. Thirteen patients were followed through two courses of Compound B, and 1 through three courses. Thus, this group of 45 patients was observed during 64 courses of Compound A and 60 courses of Compound B. Eight patients were followed only while taking Compound A, and 6 only while taking Compound B.

* All medications used in this study were furnished to us through the courtesy of the Medical Research Department of Geigy Pharmaceuticals, Div. of Geigy Chem. Corp., N. Y.

At each biweekly return visit the patient's weight, blood pressure, and pulse rate were recorded. Any side effects were noted and evaluated.

A urinalysis, hemoglobin and white blood cell count, and determination of the basal metabolic rate were done on a representative group of patients while they were taking each of the medications.

RESULTS

The average weekly rate of loss of weight for the group observed while taking each of the medications was 0.8 pounds while taking Compound A and 0.3 pounds while taking Compound B. Those observed only while taking Compound A lost on an average of 1.5 pounds a week, while those observed only while taking Compound B had a loss of 0.8 pounds. The average weekly loss of weight for all patients while taking Compound A was 0.9 pounds, and for the entire group taking Compound B was 0.3 pounds (Table 1).

After these results were obtained and recorded, we were informed that Compound A contained the active medication and Compound B was the placebo.

The pulse rate and blood pressure recorded at each visit for the entire group and determinations of the basal metabolic rate, hemoglobin, and leukocyte count on a representative group of those patients observed while taking each of the medications revealed no significant differences which could be attributed to either of the drugs (Table 2). No changes in the urinalysis were noted.

TABLE 1. Comparison of Average Weight Loss Observed with Compound A and Compound B

	Compound A (phenmetrazine)	Compound B (placebo)
Group taking each medication		
No. patients	45	45
No. courses	64	60
Average time observed (weeks)	6.5	6.4
Average weight loss (pounds per week)	0.8	0.3
Group taking only one medication		
No. patients	8	6
Average time observed (weeks)	6.9	5.9
Average weight loss (pounds per week)	1.5	0.8
Totals		
No. patients	53	51
No. courses	72	66
Average time observed (weeks)	6.6	6.3
Average weight loss (pounds per week)	0.9	0.3

TABLE 2. Clinical and Laboratory Data Obtained in 45 Subjects

	No. subjects	Phenmetrazine		Placebo	
		Range	Average	Range	Average
Blood pressure	45	108/70–200/124	142/88	104/72–204/130	142/89
Pulse rate	45	60–97	82	60–95	82
Hemoglobin (Gm.)	21	8.4–13.9	11.8	10.1–13.6	11.9
White blood cells	21	5000–13,400	7620	4350–13,850	7840
Basal metabolic rate	28	−18.5–+15	−1.7	−13–+15	−1.0

TABLE 3. Side Effects Observed

	Phenmetrazine	Placebo
Faintness and dizziness	8	4
Gas, indigestion, nausea	4	3
Headache	1	
TOTAL	13	7
No. patients receiving drug	53	51
No. patients with side effects	10 (19%)[a]	6 (12%)[b]

[a] Includes 3 patients with multiple side effects.
[b] Includes 1 patient with multiple side effects.

Side Effects

At return visits to the clinic, each patient was questioned regarding the appearance of any untoward symptoms. Any such symptom occurring at any time during the course of either of the medications was considered to be a side effect. These symptoms were recorded and tabulated (Table 3). Slightly more side effects were reported while taking Compound A (the active medication) than when Compound B was used. These side effects were referrable to the central nervous system (faintness, dizziness, headache) and the gastrointestinal system (gas, indigestion, nausea). No patient complained of insomnia. No significant differences in the incidence of gastrointestinal complaints was found between Compound A and B, and only a slightly greater incidence of symptoms referrable to the central nervous system while taking Compound A was reported. This would indicate that side effects directly attributable to phenmetrazine are not very frequent, and in no case did they necessitate discontinuance of the drug.

DISCUSSION

In this study, the caloric content of the prescribed diet was similar for all patients and was kept constant throughout the entire period of

observation. Only the medication was varied. We do not mean to imply that the greater rate of loss of weight observed while taking phenmetrazine was caused by the medication per se. We do feel, however, that this drug permitted a stricter adherence to the prescribed dietary regimen either by depressing the appetite mechanism directly or by stimulating a sense of well-being in the patient so that the symptoms of hunger were not so obvious or distressing.

SUMMARY

A group of patients were studied while taking phenmetrazine and a placebo, the dietary prescription having been kept constant, using the double blind procedure. The same patients were observed while taking each preparation, thus allowing each one to serve as her own control. The rate of loss of weight while taking phenmetrazine was more than twice that observed when a placebo was used. No significant effects upon the blood pressure, pulse rate, hemoglobin, white blood count, urinalysis, or basal metabolic rate were noted. Side effects while taking phenmetrazine were only slightly more frequent than during placebo medication.

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Antispasmodic Compound 8-88 in Relapsing Peptic Ulcer

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FOLLOWING the observations that some salts and esters of mandelic acid (phenyl oxyacetic acid) exert a paralyzing effect on the smooth muscle, new spasmolytic substances have been developed and tested pharmacologically. By introducing effective groups into the amino radicals on the aliphatic side chain, compounds were developed with increased spasmolytic potency, whereby compounds more complicated structurally proved more effective.

One of these compounds appeared to be especially effective in relieving the spasm of the smooth muscles and in exerting a potentiated papaverine-like effect[1]. This complex compound is (α-*N*-)-B-diethylaminoethyl - amino - phenylacetic acid - isoamylester hydrochloride. Pharmacologic tests have shown that the toxicity of this compound is very slight[1] and that it effectively counteracts muscle spasm caused by barium chloride, Prostigmine, or Doryl. The ability of this preparation to relieve spastic conditions in the gastrointestinal, biliary, and urogenital tract as well as bronchial spasms have been demonstrated.[2] Moreover, this substance also causes a definite increase in the flow of blood through the coronary vessels of the dog heart[3] and lowers the blood pressure in hypertensive individuals. It has been shown also to dilate the uterine cervix when used in form of a suppository, and thus to accelerate delivery.[4]

In view of these spasmolytic effects of this preparation upon the gastrointestinal tract and the well-known participation of muscular (pyloric) spasm in the symptomatology of relapses of peptic ulcer, it was of interest to determine the feasibility of extending the remission period of peptic ulcer through continuous administration of this compound during the remission period in patients with chronic relapsing peptic ulcer. In order to circumvent the well-known tendency of self-healing and spontaneous remissions of this disease, the study was done on carefully selected and notoriously relapsing cases of peptic ulcer, the rhythm of relapses of which was known for at least 2 to 3 years prior to the investigation. The preparation used was labeled Antispasmodic Compound 8-88, abbreviated as C. 8-88*.

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* R. J. Strasenburgh Company, Rochester, N. Y.

MATERIAL

The study was done on 30 patients with peptic ulcer. Of the 30 ulcers, 21 were localized in the duodenum, 3 in the stomach, 4 in the pyloric canal and 2 were marginal.* There were 13 females and 17 males, and the ages of the patients ranged from 21 to 69 years. Each of the patients studied presented a typical clinical picture of a peptic ulcer. In all cases the diagnosis was confirmed roentgenologically, and in most cases x-ray examinations were repeated several times before or during the actual study. The duration of the disease was from 2 to 29 years, with an average of 10 years from the date when the first diagnosis of the ulcer was made. Special emphasis was put on the selection of cases with great frequency of relapses and only those cases were included who presented a long history of cyclic relapses. In only 4 cases was the frequency of relapses less than one per year. In the remaining 26 cases at least one relapse, but mostly two and sometimes three and more, had been observed in each year prior to the investigation. In most of the cases the last relapse occurred in the previous year, and only in two cases of this series had a year been skipped. In 10 cases the study started during a full relapse of the disease, in 4 cases during the declining relapse, and in 16 cases during the remission period. The detailed data on the sex, age, diagnosis, duration of the disease, and frequency of relapses are listed in Table 1.

METHOD

Each patient was kept under vigilant observation for the whole duration of the investigation and reported either personally or by telephone every two weeks. Moreover, a daily record was kept by the patient regarding his symptoms and general condition on a specially printed "individual patient's card." This included daily annotations regarding the dose of each of the medications taken, the occurrence of day and night ulcer pains, discomfort in the stomach, heartburn, nausea, vomiting, black stools, constipation, dryness of mouth, difficulty in urination, dizziness, drowsiness, appetite, and the general condition. Every evening before retiring the patient checked the treatment and symptoms using "0" for those symptoms which were absent, "1" for mild symptoms, "2" for moderately severe, and "3" for very severe, which prevented him from working. General condition and appetite were indicated as follows: "G" for good, "F" for fair,

* The cooperation of Dr. J. S. Rechtschaffen in these studies is gratefully acknowledged.

TABLE 1. Data on 30 Patients with Relapsing Peptic Ulcer

Case #	Initials, sex, age	Diagnosis	Duration of disease (yr.)	Frequency of relapse
1	A. A., f, 49	Duodenal ulcer; diverticulum 2nd p. duodenum	6	8 in 6 yr. (April or July)
2	E. F., f, 36	Duodenal ulcer	2	3 in 2 yr.
3	S. G., f, 50	Duodenal ulcer	15	>20 in 15 yr.
4	A. G., f, 43	Prepyloric ulcer; antral gastritis	14	5 in the last 6 yr.
5	E. G., f, 44	Prepyloric ulcer	6	3 in the last 3 yr.
6	M. G., m, 54	Duodenal ulcer	10	4 (2 in the last yr.).
7	A. H., m, 37	Duodenal ulcer; polypous gastroduodenitis	5	2–3 a yr.
8	J. J., m, 42	Duodenal ulcer	10	5 in the last 3 yr.
9	M. J., m, 58	Duodenal ulcer; essential hypertension	13	9 in the last 7 yr.
10	W. K., m, 69	Duodenal ulcer	21	1–2 a yr. for 20 yr.
11	F. M., m, 52	Duodenal ulcer	12	2–3 a yr.
12	J. N., m, 33	Duodenal ulcer	2	3 in 2 yr.
13	A. R., m, 53	Duodenal ulcer; after gastrojejunostomy	20	3 in the last 3 yr.
14	S. S., f, 65	Marginal ulcer; after subtotal gastric resection	25	6 in the last 3 yr.
15	L. S., f, 46	Duodenal ulcer	7	5 in the last 6 yr.
16	P. S., m, 59	Duodenal ulcer; essential hypertension, coronary occlusion	29	1–2 a yr. in spring and fall since 1925.
17	S. U., f, 46	Duodenal ulcer; hypertrophic gastritis	6	2 in the last 2 yr.
18	A. W., f, 57	Pyloric ulcer; after acute perforation	2	2 in 2 yr.
19	B. Y., m, 35	Gastric ulcer	3	2 a yr.
20	B. D., f, 38	Duodenal ulcer	5	3–4 during the last yr.
21	M. G., m, 59	Duodenal ulcer, marginal ulcer; gastroenterostomy	20	Once a yr., lately constant pains.
22	N. H., m, 41	Duodenal ulcer	12	Several each yr. of several weeks' duration.
23	D. S., f, 43	Duodenal ulcer	15	1–2 each yr.
24	A. K., m, 21	Duodenal ulcer	5–6	2 in the last 4 yr.
25	L. C., f, 27	Duodenal ulcer	3	2 in the last 3 yr.
26	D. McC., m, 23	Pyloric ulcer	2	2 in 2 yr.
27	J. P., f, 42	Gastric ulcer	5	3 in 5 yr.
28	T. O'C., m, 49	Duodenal ulcer	>10	1–2 each yr. for the last 4 yr.
29	J. R., m, 51	Duodenal ulcer	6	3 during the last 2 yr.
30	O. S., m, 52	Gastric ulcer; perforation 4 years ago, repaired	4	3 during 4 yr.

and "P" for poor. Moreover, the physician in attendance was supplied with specially printed charts for each patient carrying exact record of all the recurrences and their dates, duration, symptoms, and treatment, as well as all x-ray data and the condition of the patient at the start of the treatment. The chart also contained tabulated progress notes, dates of the patient's visits to the doctor, and data regarding the dose of the medication, the diet and general regimen, complaints and signs present during treatment, complications and recurrences of the disease, and side effects observed under treatment.

In each case x-ray studies were done immediately preceding the investigation, as well as comprehensive gastric analysis, which was performed following the injection of histamine and/or insulin, according to the earlier described technic.[5] Eight to twelve hours after the last meal the Levin tube was introduced into the stomach and the position of its tip in the lowermost part of the stomach was confirmed by fluoroscopy. Two fasting specimens at an interval of 10 minutes were aspirated as completely as possible, and a dose of 0.1 cc. of histamine phosphate per 10 Kg. of weight was injected intramuscularly. The specimens were collected at intervals of 20 minutes for the first hour after injection of histamine. At the end of the first hour 16 units of regular insulin were injected intravenously and three specimens were withdrawn again every 20 minutes during the subsequent hour.

In each fraction were determined the volume of gastric juice, free and total acidity by titration with Topfer's reagent and phenolphthalein, *p*H (electrometrically), pepsin concentration (by the Glass, Pugh, and Wolf modification of Anson-Mirsky hemoglobin method[6]) and the concentration of glandular mucoprotein and mucoproteose by the method of Glass and Boyd.[7]

The gastric analysis was repeated in all the cases remaining under observation before concluding the treatment and the fractions were tested for free and total acidity, *p*H, pepsin, mucoprotein and mucoproteose, as above. Emphasis was placed on selection of intelligent and reliable patients who fully understood the requirements of close cooperation in this controlled study. All patients were given the same type of bland liberal diet, with exclusion of the food items usually forbidden in ulcer patients (spices, fried and greasy foods, roughage, strong coffee, and liquor). During periods of exacerbation patients were put on a modified Sippy or Meulengracht diet.

The dosage of C. 8-88 used was usually 1 tablet 4 times a day, and only in a few instances was this raised to 2 tablets 3 times a day.*

RESULTS

In Table 2 are listed the detailed data regarding the duration of treatment, dose, tolerance, side effects, need for other treatment, reasons why the treatment was stopped, period of disease in which the treatment with C. 8-88 was started, and its effect on the chronic manifestations of the disease, as well as the ability of the preparation to prevent another relapse.

Tolerance

C. 8-88 was, in most cases, well tolerated. In only 5 of the 30 cases did the study have to be terminated at the insistence of the patients because of symptoms of poor tolerance. These were a bad taste in the mouth after ingestion of the preparation (Case 17), heartburn (Cases 17 and 28), constipation (Cases 17 and 21), and epigastric discomfort (Case 29). In Case 4, after 11 months of good tolerance and successful treatment, the patient developed symptoms of Ménière's disease, characterized by vertigo, noise in the ears, and nausea. When the preparation was stopped the symptoms disappeared, and when the preparation was given again the symptoms reappeared. In view of this situation the treatment had to be stopped finally. No explanation can be given as to why the side effects did not occur during the first 11 months of treatment in this patient. In a few other cases complaints about the bad taste and dryness in mouth or constipation were mentioned, but they were rather mild and did not necessitate the interruption of the treatment. In the great majority of cases 4–6 tablets daily did not cause side effects like the urinary or ocular symptoms encountered during the administration of anticholinergic drugs and C. 8-88 was in general tolerated very well.

In 8 cases (Cases 2, 6, 14, 18, 25, 26, 27, and 30) the treatment had to be abandoned for various reasons before final conclusions could be reached. Patient 2 had to undergo a gynecologic operation 4½ months after the beginning of the treatment and refused to continue the treatment after that since she felt rather well. Patient 14 felt well after 3 weeks of treatment and did not want to continue. This

* The preparation was generously supplied by Dr. J. A. Morrell, Medical Director, R. J. Strasenburgh Company, Rochester, N. Y.

TABLE 2. Summary of Results of Treatment

Case #	Tolerance	Side effects	When treatment was started	Duration of treatment (mo.)	Why treatment was stopped	Effect on interval symptoms	Other treatment needed	Did relapse occur?
1	Good	None	In declining relapse	12	..	Good	Gelusil & Pro-Banthine during exacerbation of pains	No
2	Good	Bad taste, constipation	In full relapse	4½	Gynecological operation performed; patient refused to continue	Fair	Gelusil & Pro-Banthine during exacerbation of pains	Observation too short for evaluation
3	Good	Bad taste	In full relapse	9	No effect on relapse	Fair	Gelusil & Pro-Banthine during exacerbation of pains	Yes, twice (after 6 wk. & 9 mo.)
4	Good for first 10 mo.	Ménière's syndrome	In declining relapse	11	..	Good	Gelusil (for pains)	No
5	Good	Dryness in mouth	In full relapse	6½	No relief, patient refused to continue	Fair	Gelusil & Pro-Banthine for pains	Observation too short for evaluation
6	Good	None	In remission	3	Patient stopped coming	Good	None	Observation too short for evaluation
7	Good	None	In remission	12	..	Good	Skopolate, if needed, for pains	No
8	Good	None	In full relapse	12	..	Good	Gelusil & Pro-Banthine occasionally	No
9	Good	Constipation	In declining relapse	12	..	Fair	Gelusil & Skopolate for pains	No, but short periods of discomfort
10	Good	None	In remission	11½	..	Good	Skopolate, rarely, for pains	No
11	Good	None	In remission	12	..	Good	Gelusil for first 3 mo.	No
12	Good	None	In remission	13	..	Good	Antacids, if needed	No
13	Good	None	In remission	12	..	Fair	Pro-Banthine or Skopolate in relapses	Yes, twice (after 4 & 8 mo.)

TABLE 2.—*Continued.* Summary of Results of Treatment

Case #	Tolerance	Side effects	When treatment was started	Duration of treatment (mo.)	Why treatment was stopped	Effect on interval symptoms	Other treatment needed	Did relapse occur?
14	Good	None	In full relapse	3 wk.	Felt well, didn't want to continue	Good	None	Observation too short for evaluation
15	Good	None	In remission	13	..	Good	None	No
16	Good	None	In remission	12	..	Good	Pamine or Gelusil for pains	No
17	Poor	Bad taste, heartburn, constipation	In remission	3½	Because of side effects	Good	None	Observation too short for evaluation
18	Good	None	In remission	2	Hostility to physician	Good	None	Observation too short for evaluation
19	Good	None	In relapse	6	Stopped coming	Good	Gelusil for heartburn and pain	Observation too short for evaluation
20	Good	None	In relapse	12	..	Good	Amphojel & Antrenyl in first months	No
21	Good	Constipation	In remission	1 wk.	Because of constipation	..	..	No
22	Good	Dryness in mouth	In relapse	11½	..	Good	Skopolate during first 2 weeks	No
23	Good	None	In declining relapse	12½	..	Good	None	No
24	Good	None	In remission	8½	..	None	None	Yes
25	Good	None	In relapse	2	..	..	None	Observation too short for evaluation
26	Good	None	In remission	1	Tired of bookkeeping	..	None	Observation too short for evaluation
27	Good	None	In remission	2½	Tired of taking medication	Good	None	Observation too short for evaluation
28	Poor	Heartburn	In remission	1½	Because of side effects	Fair	Gelusil for heartburn	Observation too short for evaluation
29	Poor	Epigastric discomfort	In remission	3½ wk.	Because of side effects	..	Gelusil	Observation too short for evaluation
30	Good	None	In full relapse	1	No relief	..	None	Observation too short for evaluation

same patient developed a new relapse a few months later and had to be operated on for marginal ulcer. Patient 18 developed hostility to the physician and refused to carry on. Patient 6 simply stopped coming, without giving a reason. Patients 26 and 27 refused to continue the treatment because of having to make notes and take medication four times a day. Patient 25 stopped coming 2 months after start of treatment. In Case 30 the treatment had to be stopped after 1 month because of lack of relief during the period of fullblown relapse.

In 14 cases the treatment and observation was continued for 11–13 months without any difficulties. These cases form the basis for evaluation of the effects of C. 8-88 on prevention of relapses.

Effect on Blood Pressure

In view of the reported effect of C. 8-88 on lowering high blood pressure, in all cases studied blood pressure was measured during the treatment. In no patient with normal or low blood pressure did we note any decrease of blood pressure following treatment with C. 8-88. Only in two patients (Cases 9 and 16) whose blood pressure was increased, (170–180/110 mm. and 210–220/130 mm. respectively) did we find slight tendency to a lower level under the effect of C. 8-88. The decrease in the systolic pressure did not exceed 30–40 mm. Hg, and that in the diastolic of 8–20 mm.

Effects in the Interval Stage

In all the 16 cases tabulated in Table 2 (Cases 1, 3, 4, 7, 8, 9, 10, 11, 12, 13, 15, 16, 20, 22, 23, and 24) the effectiveness of C. 8-88 was uniformly good upon the slight epigastric discomfort, pressure and heaviness, and disturbing feeling of hunger or heartburn which occurred occasionally during the interval stage of disease. Many patients stated that while on C. 8-88 they did not have to employ any additional preparation to keep them comfortable (Cases 10, 11, 12, 15, 16, and 23). However, when the symptoms increased in intensity, C. 8-88 did not suffice and antacids and/or anticholinergic drugs became necessary (Cases 1, 3, 4, 5, 7, 8, 9, 15, 19, 20, and 22).

Effects in the Acute Stage

Our observations indicate that C. 8-88 is inadequate in acute stage of disease or in a fullblown recurrence. Apparently its effects upon the ulcer pain, gastric motility, and secretory function of the stomach are not sufficient to counteract or abolish ulcer distress. In each instance when this was the case, the addition of antacids and potent

anticholinergic drugs was extremely helpful in rapid alleviation of the distress.

Effects Upon Recurrences

This effect was evaluated on the basis of data collected in 16 cases of peptic ulcer in whom the 11–13 mo. observation period was concluded (Cases 1, 4, 7, 8, 9, 10, 11, 12, 13, 15, 16, 20, 22, and 23), or in whom the relapse occurred before the year (Cases 3 and 24). Of the 16 cases, in 3 a relapse was not prevented by continuous administration of C. 8-88. In Case 3 the relapse occurred twice during administration of C. 8-88, 6 and 9 months after the beginning of the treatment. In Case 13, the relapses occurred during the fourth and eighth months of the treatment, and were associated each time with a severe melena and recrudescence of pains. Moreover, Patient 9 from time to time suffered from short periods of epigastric discomfort for several days while on C. 8-88 treatment, but was markedly improved after switching to C. 8-88 plus antacids. On the other hand, Patient 24 felt well for 7 months on C. 8-88 but developed a relapse 1½ months after he was switched to C. 8-88 with antacids.

The remaining 12 patients (Cases 1, 4, 7, 8, 10, 11, 12, 15, 16, 20, 22, and 23) had no relapse during the observation period of 11–13 mo. while they were treated daily with C. 8-88. For the patients this was extremely satisfactory, since each of them had at least one and most frequently two relapses during each year prior to C. 8-88 treatment. Case 1 had eight relapses during the last 6 years; Case 8, five relapses in the last 3 years; Case 9, nine relapses in the last 7 years; Case 11, two to three relapses each year during the last 12 years; Case 12, three relapses during the last 2 years; Case 20, three or four relapses during the last year; and Cases 22 and 23, at least two but often more relapses during each of the last 12 to 15 years. Since no recurrences were observed in these cases for 1 year, and all the other elements of the environment, diet, and general life situation remained the same in these 9 patients, it appears that in these cases the treatment with C. 8-88 contributed to the prolongation of the remission period of the disease.

Effect on Gastric Secretion

In 13 patients who were under close observation for at least 6 months, we studied the effect of prolonged treatment with C. 8-88 upon gastric secretion. We used the method of comprehensive study of gastric secretion,[5] as described previously. All the tests were per-

TABLE 3. Gastric Analysis in Nine Cases of Duodenal Ulcer Before and After Treatment with C. 8-88

Case #	Initials, sex, age	Gastric juice	Before treatment							After treatment						
			Fasting	After histamine[a]			After insulin[b]			Fasting	After histamine[a]			After insulin[b]		
				20′	40′	60′	20′	40′	60′		20′	40′	60′	20′	40′	60′
11	F. M., m, 52	Volume (cc.)	55	72	52	7	12	24	62	40	68	64	16	10	31	50
		pH	1.52	1.38	1.29		1.38	1.41	1.38	..	..	..	..	..	..	..
		Free acid (mEq./L.)	51	86	97	72	65	72	92	50	74	88	80	66	70	88
		Total acid (mEq./L.)	64	103	106	83	77	83	105	66	90	100	96	75	85	101
		Pepsin (PU^{Hb}/cc. × 10^4)	116	125	118	100	124	188	179	100	116	116	68	101	175	181
		Muoprotein (mg./100 cc.)	55	81	77	69	70	146	140	84	90	91	60	85	189	180
		Muoproteose (mg./100 cc.)	122	92	98	112	125	118	98	160	75	70	110	90	110	95
5	E. G., f, 44	Volume (cc.)	15	40	15	10	..	50	50	30	35	20	12	8	35	40
		Free acid (mEq./L.)	30	65	64	41	..	51	105	40	48	72	90	10	65	70
		Total acid (mEq./L.)	39	72	70	50	..	60	141	50	56	80	66	25	75	84
		Muoprotein (mg./100 cc.)	135	90	114	108	..	193	196	108	120	84	65	40	220	208
		Muoproteose (mg./100 cc.)	71	38	76	45	..	87	54	105	100	86	80	121	160	140
6	M. G., m, 54	Volume (cc.)	24	45	19	12	6	32	44	16	50	24	20	10	40	64
		Free acid (mEq./L.)	13	55	72	33	15	37	95	18	65	70	42	8	70	102
		Total acid (mEq./L.)	23	67	84	44	25	50	102	30	78	82	56	20	84	110
		Pepsin (PU^{Hb}/cc. × 10^4)	80	76	74	65	42	96	180	110	84	106	84	40	160	212
7	A. H., m, 37	Volume (cc.)	16	40	28	16	8	25	41	22	42	22	24	12	30	32
		Free acid (mEq./L.)	8	77	95	78	52	81	98	14	65	95	80	40	90	105
		Total acid (mEq./L.)	18	83	102	84	63	88	106	20	75	103	94	52	98	115
		Pepsin (PU^{Hb}/cc. × 10^4)	60	135	125	66	120	170	230	66	98	13	60	106	150	242
16	P. G. m, 59	Volume (cc.)	50	100	70	32	10	62	..	35	64	46	40	12	45	..
		pH	1.89	1.51	1.32	1.19	1.30	1.49	..	..	..	..	..	..	..	..
		Free acid (mEq./L.)	26	56	89	96	59	34	..	12	64	95	90	64	42	..
		Total acid (mEq./L.)	33	65	98	108	75	44	..	20	80	106	102	76	52	..
		Pepsin (PU^{Hb}/cc. × 10^4)	46	76	87	89	141	73	..	40	102	90	84	60	220	..
		Muoprotein (mg./100 cc.)	44	74	85	85	146	86	..	50	90	64	60	66	190	..
		Muoproteose (mg./100 cc.)	62	51	41	64	208	102	..	120	86	80	64	144	180	..

TABLE 3.—Continued. Gastric Analysis in Nine Cases of Duodenal Ulcer Before and After Treatment with C.8-88

Case #	Initials, sex, age	Gastric juice	Before treatment							After treatment						
			Fasting	After histamine[a]			After insulin[b]			Fasting	After histamine[a]			After insulin[b]		
				20′	40′	60′	20′	40′	60′		20′	40′	60′	20′	40′	60′
12	J. N., m, 33	Volume (cc.)	32	47	63	33	..	35	16	24	16	58	20	20	40	12
		Free acidity (mEq./L.)	24	47	89	89	..	80	8	20	50	92	100	42	96	26
		Total acidity (mEq./L.)	38	60	98	100	..	97	24	35	62	102	110	50	112	40
		Pepsin (PU^{Hb}/cc. × 10^3)	176	141	118	140	..	241	141	140	180	155	152	110	260	160
		Mucoprotein (mg./100 cc.)	158	129	93	117	..	189	115	102	104	66	124	80	210	135
		Mucoproteose (mg./100 cc.)	135	61	59	39	..	66	117	260	84	76	80	120	140	160
15	L. S., f, 46	Volume (cc.)	30	27	31	28	57	130	80	22	26	35	30	60	124	60
		Free acidity (mEq./L.)	16	90	54	33	90	134	136	12	88	66	45	110	130	140
		Total acidity (mEq./L.)	28	98	63	42	102	139	144	20	98	75	55	118	145	132
		Mucoprotein (mg./100 cc.)	122	134	63	74	165	371	186	80	120	46	60	230	250	226
		Mucoproteose (mg./100 cc.)	105	69	66	71	164	74	82	210	86	80	76	190	112	120
8	J. J., m, 42	Volume (cc.)	69	79	40	21	18	29	77	45	60	44	25	21	35	50
		pH	1.91	1.21	1.21	2.00	1.73	1.21	1.10	1.90	1.20	1.10	1.32	1.52	1.15	0.97
		Free acidity (mEq./L.)	27	80	81	18	27	80	107	30	81	95	72	50	93	133
		Total acidity (mEq./L.)	37	85	86	25	38	89	115	43	90	105	82	61	100	143
		Pepsin (PU^{Hb}/cc. × 10^3)	88	81	55	55	135	195	162	90	102	70	76	134	162	158
		Mucoprotein (mg./100 cc.)	160	77	66	76	137	215	174	..	..	..	..	..	..	..
		Mucoproteose (mg./100 cc.)	90	67	60	137	119	132	95	..	..	..	..	..	..	..
17	S. U., f, 46	Volume (cc.)	42	30	..		7	19	32	36	40	..		18	18	27
		pH	1.90	1.28	..		1.45	1.21	1.11	..	..	..		..	..	..
		Free acidity (mEq./L.)	23	65	..		30	47	108	25	72	..		12	35	103
		Total acidity (mEq./L.)	32	69	..		35	52	112	35	79	..		18	45	110
		Pepsin (PU^{Hb}/cc. × 10^3)	82	98	..		90	235	218	76	88	..		60	210	176
		Mucoprotein (mg./100 cc.)	74	125	..		120	278	286	36	98	..		80	240	256
		Mucoproteose (mg./100 cc.)	136	167	..		108	252	210	210	160	..		84	176	160

[a] 0.1 cc. histamine phosphate per 10 kg. body weight, subcutaneously.
[b] 16 units regular insulin, intravenously.

TABLE 4. Gastric Analysis in Four Cases of Duodenal Ulcer Before and After Treatment with C. 8-88

Case #	Initials, sex, age,	Gastric juice	Before treatment							After treatment						
			Fasting	After histamine[a]				After insulin[b]			Fasting	After histamine[a]				After insulin[b]		
				15′	30′	45′	60′	20′	40′	60′		15′	30′	45′	60′	20′	40′	60′
2	E. F., f, 36	Volume (cc.)	30	30	40	25	17	8	8	30	22	41	58	16	21	..	..	..
		pH	1.81	1.30	1.30	1.36	1.48	2.28	1.30	1.21	..	..	..	..	..	..	..	..
		Free acidity (mEq./L.)	37	72	97	61	48	13	57	79	42	68	102	60	56	..	..	..
		Total acidity (mEq./L.)	52	86	108	77	68	30	77	92	51	80	112	80	65	..	..	..
		Pepsin (PU^{Hb}/cc. × 10^4)	142	114	111	101	132	166	222	204	108	116	135	64	48	..	..	..
		Mucoprotein (mg./100 cc.)	151	115	119	115	179	168	278	217	104	108	160	108	112	..	..	..
		Muceproteose (mg./100 cc.)	270	115	98	158	127	276	222	200	112	125	64	150	162	..	..	..
3	S. G., f, 50	Volume (cc.)	13	9	11	39	..	..	..	..	10	8	16	60	..	..	..	..
		pH	1.86	1.30	1.33	1.41	..	..	..	..	1.75	1.27	1.24	1.25	..	..	..	..
		Free acidity (mEq./L.)	22	37	55	43	..	..	..	..	26	42	54	50	..	..	..	..
		Total acidity (mEq./L.)	33	39	63	51	..	..	..	..	35	60	65	58	..	..	..	..
		Pepsin (PU^{Hb}/cc. × 10^4)	156	131	117	149	..	..	..	..	140	150	126	118	..	..	..	..
		Mucoprotein (mg./100 cc.)	137	117	91	118	..	..	..	..	145	110	86	84	..	..	..	..
		Muceproteose (mg./100 cc.)	121	86	76	92	..	..	..	..	220	210	108	64	..	..	..	..
22	N. H., f, 41	Volume (cc.)	33	33	65	50	21	24	25	47	26	20	50	46	25	30	30	55
		pH	1.71	1.18	1.11	1.09	1.15	1.25	1.41	1.19	..	..	..	..	..	..	..	..
		Free acidity (mEq./L.)	23	75	85	89	73	40	20	68	16	50	88	75	62	16	40	79
		Total acidity (mEq./L.)	32	82	89	95	75	45	25	73	28	58	95	83	80	22	50	86
		Pepsin (PU^{Hb}/cc. × 10^4)	134	134	117	103	135	115	230	229	120	118	80	76	48	62	196	189
		Mucoprotein (mg./100 cc.)	119	141	96	92	135	129	216	166	..	..	..	..	..	..	..	..
		Muceproteose (mg./100 cc.)	265	246	127	93	102	194	221	166	..	..	..	..	..	..	..	..
13	A. R., m, 53	Volume (cc.)	5	29	30	104	79	..	..	..	12	15	25	64	45	..	..	..
		pH	8.00	1.30	1.38	1.68	1.80	..	..	..	..	..	..	..	..	..	..	..
		Free acidity (mEq./L.)	0	70	63	38	33	..	..	..	0	68	70	52	26	..	..	..
		Total acidity (mEq./L.)	2	80	70	45	38	..	..	..	5	80	76	60	38	..	..	..
		Pepsin (PU^{Hb}/cc. × 10^4)	3	114	76	100	140	..	..	..	0	80	66	88	99	..	..	..
		Mucoprotein (mg./100 cc.)	18	98	58	67	97	..	..	..	10	65	64	75	86	..	..	..
		Muceproteose (mg./100 cc.)	450	118	110	69	95	..	..	..	385	160	140	29	64	..	..	..

[a] 0.1 cc. histamine phosphate per 10 kg. body weight subcutaneously.
[b] 16 units regular insulin intravenously.

formed under similar basic conditions, and the data obtained are listed in Tables 3 and 4.

The data indicate that continuous treatment with C. 8-88 does not influence the secretory pattern of the stomach in a uniform way. The volume of gastric secretion as well as free and total acidity show similar patterns in most of the cases studied, both before and after treatment. Some moderate deviations from the base line (plus or minus) observed following treatment with C. 8-88 did not show any uniform trend of statistical significance. The same applies to the *p*H of the gastric juice, which also did not show any uniform changes after prolonged administration of C. 8-88. Apparently the increase in gastric acidity occurring after histamine or insulin stimulation is not blocked by the treatment with C. 8-88.

The patterns of other secretory products of the gastric glands—pepsin and glandular mucoprotein—also fail to show any uniform modifications as result of treatment with C. 8-88. Previous investigations have demonstrated that the secretion of these components is strongly influenced by central vagal stimulation, so that their concentration in the gastric juice increases markedly following intravenous injection of insulin. It is clear from data obtained in the present investigations and listed in Tables 3 and 4 that the stimulatory effect of central nervous stimulation upon the secretion of pepsin and glandular mucoprotein is not blocked by the prolonged administration of C. 8-88, in contrast to typical anticholinergic drugs, which block the secretion of these substances following insulin stimulation.[8, 9] This indicates that C. 8-88 does not exert a significant anticholinergic effect upon the stomach of patients with peptic ulcer, and that its effect upon the clinical course of this disease is not mediated through its effect upon gastric secretion. This is in line with the absence of anticholinergic effect and lack of significant untoward effects of the drup upon the individuals treated for 1 year with C. 8-88.

CONCLUSIONS

The interval treatment of chronic relapsing peptic ulcer of the stomach and duodenum with Antispasmodic Compound 8-88 appears to extend the duration of the remission period (over 1 year) in a large percentage of cases.

This therapeutic effect does not result from a decrease of the secretory activity of the gastric glands, since no significant changes in the output of gastric juice and all the glandular secretory products of the

stomach (acid, pepsin, mucoprotein) were observed following this treatment.

Anticholinergic drugs and antacids are more effective than Compound 8-88 in the treatment of peptic ulcer during the period of relapse.

The tolerance to the treatment with Compound 8-88 in a daily dose of 50 mg. 4 times a day or 100 mg. 3 times a day was good and side effects were slight.

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Belladonna Alkaloid-Sedative Mixture

Effects on gastric acidity and motility

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CONTROVERSY still exists as to the causative factor of pain in peptic ulceration. Some believe that acid is the *sine qua non* in the production of pain. This belief started with the demonstration by Boniger[1] that the introduction of 0.1N hydrochloric acid into the stomach of a patient with active peptic ulcer would produce typical pain. It was supported later by Palmer and his coworkers[2] and by Bonney and Pickering.[3] Others felt that pain was the result of increased motility and spasm,[4] and still others that pain was produced by the acid-causing spasm in or near the ulcer site. Studies by Ruffin and associates, however, showed that the relief of pain after vagotomy[5] and following methantheline bromide[6] was apparently due mainly to effects on motility rather than on acidity. They also felt that elevation of the pain threshold will relieve ulcer pain, a mechanism through which sedatives and narcotics seem to work.

While there exists controversy as to the cause of pain in peptic ulcer, it is generally assumed that spasm of smooth muscle is the cause of pain experienced by patients with functional digestive disorders. Hence, the use of antispasmodic substances as an adjuvant therapeutic agent has become an established practice in the treatment of diseases of the digestive tract, whether they are on an organic or functional basis.

For many years the belladonna alkaloids were the only anticholinergic drugs available. These were of limited value when employed singly, partly because the clinically effective dose, as determined by objective tests, was frequently associated with certain undesirable side effects such as xerostomia and mydriasis. While the effects upon accommodation of the eye and upon intraocular pressure are produced by local instillation, actual disturbances in vision are rarely if ever

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encountered from oral administration of the alkaloids. Diminished salivary secretion is probably the earliest and most conspicuous side effect; in reality it is a safeguard against overdosage. The principal alkaloid of belladonna, *l*-hyoscyamine, is seldom employed in clinical practice, probably because of its tendency to undergo spontaneous racemization under varying conditions of storage and in certain types of pharmaceutical preparations. Stabilization may be accomplished by conversion with racemic atropine or by the presence of the other natural alkaloids in the proper amounts to create a stable equilibrium state. The presence of hyoscine, or scopolamine, contributes certain desirable actions which are not observed in the use of hyoscyamine alone.

In recent years many different antispasmodic mixtures and many cholinergic blocking agents have been introduced and studied experimentally and clinically. These studies demonstrated that besides their clinical symptomatic effect some of them had a definite inhibitory effect on gastric motility and acidity.[7]

In this paper the results of our studies—experimental and clinical—with a mixture of natural belladonna alkaloids with phenobarbital* are being reported. The antisecretory and antimotility effect was studied in ulcer patients and the relationship between acidity and motility noted. The clinical effects were observed on patients with abdominal symptoms who fell into the following diagnostic categories: (a) duodenal or (b) gastric ulcer, (c) irritable bowel which included hypertrophic gastritis, pylorospasm, postcholecystectomy syndrome, duodenitis, diverticulosis and diverticulitis, (d) ulcerative colitis, (e) amebiasis, (f) gallbladder disease, and (g) postoperative cases of carcinoma of the colon.

MATERIAL AND METHODS

The data which form the basis of this report were acquired from observations upon 176 patients (Table 1), 29 of whom were hospitalized and 147 were patients seen in the gastrointestinal clinic or private office. Of the 29 hospitalized patients 11 had peptic ulcer (9 duodenal and 2 gastric), 1 had gallbladder disease, and 17 had functional disorders of the gastrointestinal tract.

Of the 176 patients, 86 were males and 90 females. The ages ranged among the males from 14 to 75, with an average of 43 years, and

* Donnatal. Supplied to us through the courtesy of William R. Bond, M.D., Director of Clinical Research, A. H. Robins Company, Inc., Richmond, Va.

TABLE 1. Patients Given Donnatal

Diagnosis	Number treated		
	Male	Female	Total
Duodenal ulcer	48	20	68
Gastic ulcer	8	2	10
Irritable bowel	19	47	66
Ulcerative colitis	6	8	14
Amebiasis	4	3	7
Gall bladder disease	0	6	6
Postoperative, colon carcinoma	1	4	5
TOTAL			176

among the females from 17 to 78, with an average of 34 years. There were 12 Negro patients (9 females and 3 males, of whom 6 had peptic ulcer and 6 irritable bowel).

The most common symptoms in these patients were, in order of frequency: abdominal pain, epigastric pain, abdominal discomfort, abdominal cramps, "gas" pain (distention, flatulence, bloating, eructation), nausea, emesis, diarrhea, food intolerance, anorexia, pyrosis, hematemesis, weakness, hunger pain, and precordial pain.

All patients had complete preliminary gastrointestinal workup, including gastric analysis, stool examination, and x-ray studies of the upper and/or lower gastrointestinal tract. The ultimate diagnosis was based on the results of the history and physical examination and laboratory workup.

Fifty of these cases underwent repeated fractional gastric analysis to study the antisecretory effect of the antispasmodic-sedative mixture on the stimulated and unstimulated stomach. Fifteen patients had motility studies according to the procedure to be described. Of these, 3 were used as controls without any medication, 2 receiving a placebo of water and lactose tablets and one receiving nothing by mouth. Twelve had motility studies while receiving 2 tablets of Donnatal.

Antisecretory Study

This study was done on two groups. Each patient was tested on 2 days. Patients with duodenal or gastric ulcer or with hypertrophic gastritis were fasted for 12 hours. The following morning they were intubated and 4 specimens of gastric juice aspirated at 15-minute intervals. The free and total acidity was determined in each of the specimens, and the results served as the base line for the control period.

In one group the acidity was determined on the first day for 135

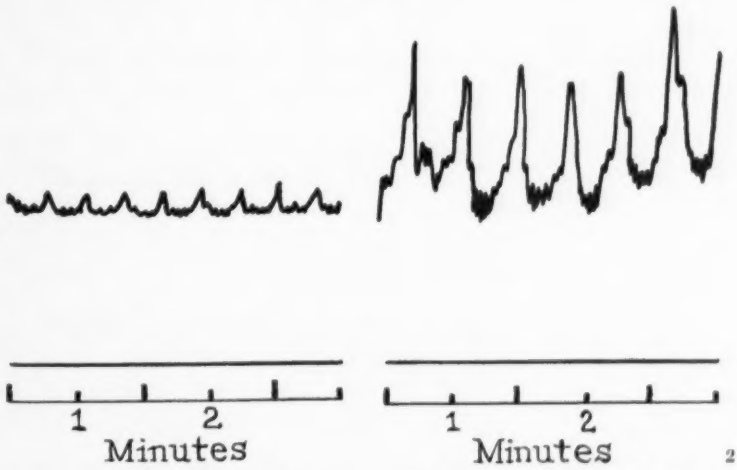
minutes in the unstimulated stomach. On the second day the patient received 2 tablets of Donnatal after the fourth aspiration and the test was continued for 90 minutes. This enabled us to compare the acidity curves on days with and without Donnatal (see Fig. 3) in the unstimulated stomach.

In the second group the patients received on the first day an injection of histamine, 0.01 mg./Kg. body weight, after the fourth aspiration and the aspirations were continued. On the second day they received, after the fourth aspiration, an injection of histamine and 2 tablets of Donnatal orally at the same time, and the aspirations were continued at 15-minute intervals for the next 90 minutes. This made it possible to observe the effect of Donnatal on the histamine-stimulated stomach (see Fig. 4).

Motility Studies

The motility studies were preceded by a fasting period of 8–12 hours. All experiments were carried out in a quiet room with the subjects in a comfortable recumbent position. In order to reduce or eliminate possible anxiety and tension on the part of the patients, they were instructed in advance as to the nature of the procedure.

A Miller-Abbott tube with an attached balloon of about 50 cc.



1 2

Fig. 1. **Low-amplitude waves of antral motility which we considered as Type 1.**
Fig. 2. **Higher amplitude waves of antral motility which we considered as Type 2.**

capacity was passed into the stomach and placed in the antrum. The position of the balloon was checked by fluoroscopy. With the balloon in the correct position the tube was fixed to the face with adhesive tape and connected to the water manometer. The balloon was then inflated with 20 cc. of air. Changes in the pressure in the balloon were recorded on the moving kymograph paper which moved at a speed of 2 cm. per minute.[8] After a control period of approximately 40 minutes the test substance (Donnatal) was administered orally; the time was marked on the moving graph paper and the motility recorded for the following 2–2½ hours. The subjects were observed closely and all abnormal waves due to movements or cough were marked.

The control recordings, with placebo given at the end of the control period, were carried out in an identical way.

The graphs were analyzed according to the generally observed two main types of motility waves, which are usually used for evaluation of tracings:

Type I, low-amplitude waves, occurring either rhythmically or not; when rhythmically, their frequency was about 3 per minute (Fig. 1).

Type II, sharp-peaked, tall waves of varying duration and amplitude, also appearing in a rhythmical or nonrhythmical pattern (Fig. 2).

Observation Periods

The observation time was divided into two main periods of activity of antral contractions.

Control period, lasting approximately 40 minutes, in order to get optimally stabilized tonus of contractions. This period was followed by

Postmedication period, beginning with the moment when the drug was administered and lasting until the end of the experiment. This period was subdivided into

Latent period, which was identified as that period between the time when the medication was given and the time of the onset of the response.

Response period, which designated the period during which the changes in the motility continued.

Rebound period, which was the period when the motility curve seemed to regain its premedication character.

Clinical Study

The patients received 1 tablet of Donnatal before meals and at bedtime. If the symptoms remained unchanged the results were

classified as *Poor*; if the symptoms were partially relieved the results were classified as *Fair*; and if the symptoms were completely relieved within a short time and persisted thus, the results were classified as *Good*.

Concurrent Treatment

The peptic ulcer patients received, in addition to the ulcer diet and antacids, the antispasmodic-sedative mixture Donnatal. The patients with ulcerative colitis received in addition to the ulcerative colitis diet various other medications (antibiotics, sulfonamides, and occasionally steroids) and blood transfusions. The patients with amebiasis received, in addition to an appropriate diet, specific antiamebic therapy. The patients grouped under the heading of the irritable bowel and the postoperative patients received only an appropriate diet in addition to the test substance. Many of these patients had been previously on one or the other of the antispasmodics currently used with only little or no relief, so that their subjective symptoms both as to therapeutic efficacy and side effects were considered as a measure of the benefit or failure of the test substances.

Evaluation of Progress

The hospital patients who were put on this regimen were interviewed daily during the hospital rounds as to their symptoms. The outpatients from the gastrointestinal clinic or those seen in private practice who received these substances were interviewed first at weekly and later at biweekly intervals, after amelioration of symptoms; they were questioned as to how they felt, and, based upon their answers as to the persistence or absence of symptoms, their clinical progress was evaluated. Some patients were kept on the medication from 2 to 4 weeks. Others took it for a much longer period; most of the ulcer patients took the medication for 3 months or more in accordance with our policy of giving such patients antispasmodics and antacids for several months. A few patients have taken the antispasmodic-sedative mixture for over 1 year.

If no relief of symptoms had occurred within one week, the particular test substance was discontinued and replaced with another substance. At times, however, the dosage would be increased and continued for another week. Similarly, if untoward symptoms had occurred with the test substance, this particular drug was also discontinued. Slight dryness of the mouth, metallic taste, mild heartburn, etc., were considered as minor side effects and ignored. Severe dry-

ness of the mouth, eye symptoms, constipation, and urinary retention were believed sufficient indication for discontinuation of the particular test substance.

RESULTS

Antisecretory Responses

The results obtained during the antisecretory study with Donnatal are presented in Figs. 3 and 4. Briefly, it may be stated that the patients in whom the stomach was not stimulated showed a slight decrease in their gastric acidity on the day when they received Donnatal, as compared to the control day when they received nothing. The patients in whom the stomach was stimulated by the injection of a dose of histamine showed no appreciable difference in the gastric secretory curve on the day when histamine was given alone as compared to the days when histamine and Donnatal were given simultaneously.

One might therefore conclude that a larger dose of Donnatal is

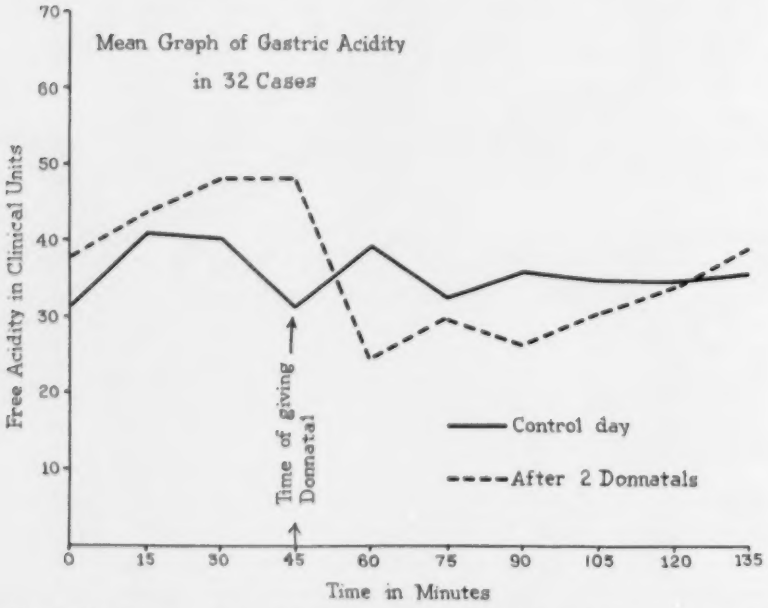


Fig. 3. **Mean graph of gastric acidity in 32 ulcer patients who received no medication on the control day and 2 Donnatal tablets on the test day.**

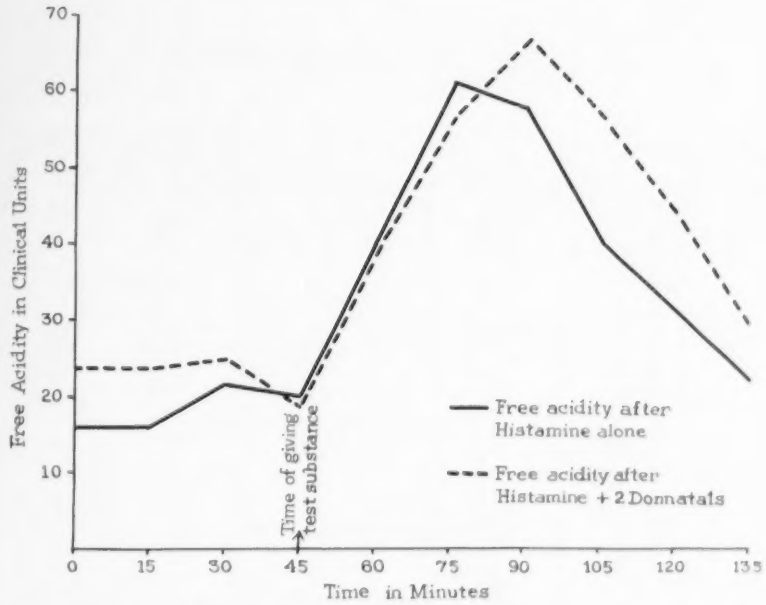


Fig. 4. **Mean graph of gastric acidity in 18 ulcer patients who received an injection of histamine 45 minutes after the start of the experiment on the control day and an injection of histamine simultaneously with 2 tablets of Donnatal on the test day.**

necessary to decrease histamine-induced gastric secretion, and there is no reason to believe that this larger dose would not be effective.

Motility

Following the ingestion of 2 tablets of Donnatal the antral motility decreased in 8, remained unchanged in 3, and was equivocal in 1 (Table 2). An example of the motility curves is presented in Figs. 5 and 6.

Following the ingestion of the test medication there was a latent period of 3–70 minutes, with an average of about 30 minutes. The depression of the motility persisted in 6 patients until the end of the experiment. Two cases showed a return to previous active contraction following the response period.

Of the control cases, 2 had no change and 1 an increase in the motility (Table 3 and Fig. 7).

TABLE 2. Antral Motility in 12 Subjects Who Received 2 Tablets of Donnatal

Name	Sex	Age	Control period		Postmedication period						Total duration of experiment (min.)
					Latent period		Response period		Rebound period		
			Duration (min.)	Type of waves	Duration (min.)	Type of waves	Duration (min.)	Type of waves	Duration (min.)	Type of waves	
J. L.	M	18	38	I	17	II	91	I	0	0	146
J. L.	M	32	39	II	74	II	33	I	0	0	146
D. J.	M	67	44	I	N.C.	I	N.C.	I	0	0	151
W. J.	M	66	41	II	34	II	45	I	0	0	120
K. B.	M	46	37	II	3	II	98	I	0	0	138
B. V.	M	65	38	II	23	II	58	I	38[a]	II	157
F. A.	M	40	38	II	42	II	47	I	0	0	127
S. A.	M	31	40	I	N.C.	I	N.C.	I	0	0	100
R. S.	M	70	40	II	6	II	30	I	15[a]	II	110
McL R.	F	38	39	I	N.C.	I	N.C.	I	0	0	120
R. J.	M	39	42	II	44	II	44	I	0	0	130
S. T.	M	65	54	II	60	II	15	I	0	0	129

0—No rebound period.
N.C.—No change.
[a] End of the experiment.

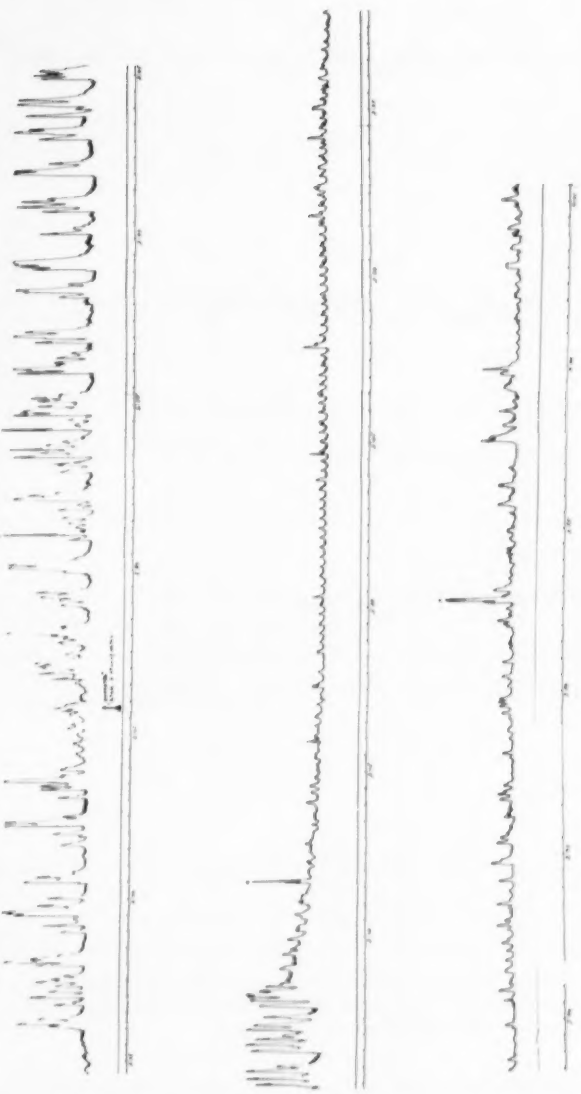


Fig. 5. **Motility curve of antral motility in an ulcer patient during the control period and following the ingestion of 2 tablets of Donnatal. This patient had initially very high waves.**

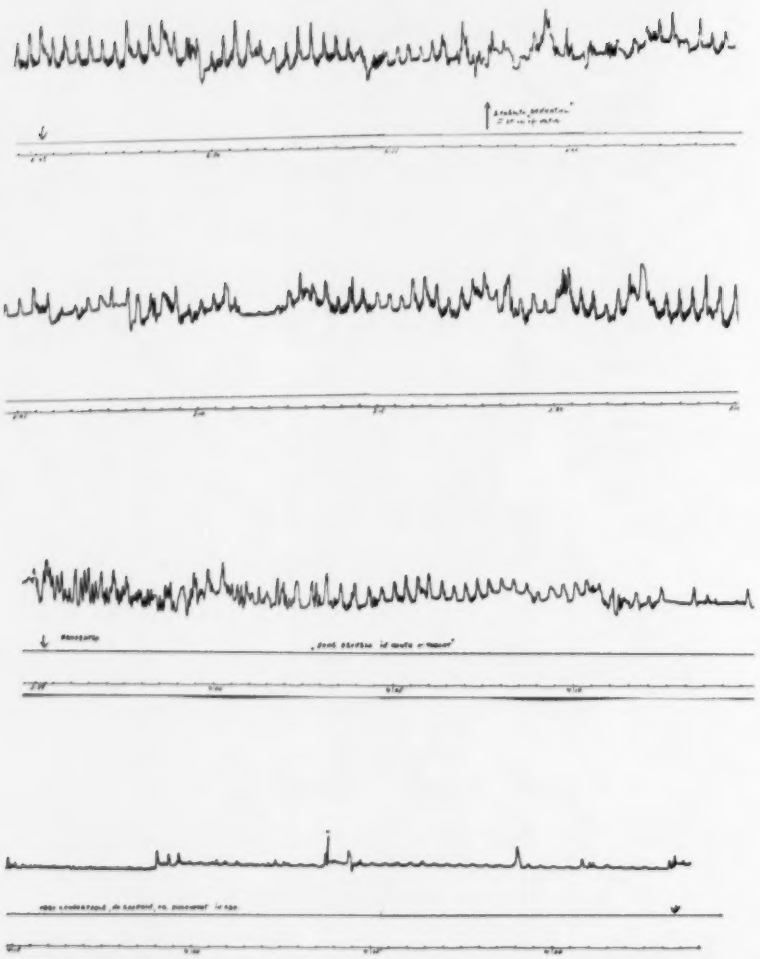


Fig. 6. **Motility curves of the antrum in an ulcer patient during the control period and following the ingestion of 2 tablets of Donnatal. This patient had initially lower waves and a long latent period.**

Clinical Results

The clinical results of the Donnatal medication are presented in Table 4. It is evident that almost 80 per cent of the duodenal ulcer patients, whether male or female, had good results; and only 5 per

TABLE 3. Antral Motility in 3 Control Subjects

Name	Sex	Age	Control period		Postmedication period						Total duration of experiment (min.)
					Latent period		Response period		Rebound period		
			Duration (min.)	Type of waves	Duration (min.)	Type of waves	Duration (min.)	Type of waves	Duration (min.)	Type of waves	
F. H.[a]	M	37	40	I	N.C.	II	N.C.	II	0	0	100
B. R.[a]	M	56	41	I	27	I	60	II	0	0	128
Y. A.[b]	M	53	N.C.	I	N.C.	I	N.C.	I	0	0	85

N.C.—No change.
0—No rebound period.
[a] Placebo.
[b] No Medication or placebo.

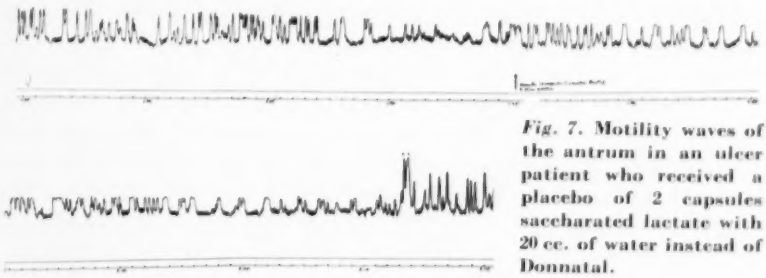


Fig. 7. **Motility waves of the antrum in an ulcer patient who received a placebo of 2 capsules saccharated lactate with 20 cc. of water instead of Donnatal.**

TABLE 4. Results of Donnatal Treatment

Diagnosis	% Good		% Fair		% Poor	
	Male	Female	Male	Female	Male	Female
Duodenal ulcer	77	80	19	15	4	5
Gastric ulcer	75	100	25	..	..	..
Irritable bowel	53	58	37	34	10	8
Ulcerative colitis	67	75	33	25	..	..
Amebiasis	75	33	25	67	..	..
Gallbladder disease	..	100	..	..	..	..
Postoperative, colon carcinoma	100	75	..	..	..	25

cent poor results. Most of the gastric ulcer patients also had good results. Among the patients with irritable bowel, however, only about 53 per cent of the male and 58 per cent of the female had good results; and 10 per cent of the male and 8 per cent of the female patients had

poor results. Similarly, the percentage of good results was 67 (male) and 75 (female), in the cases of ulcerative colitis, while 75 per cent of the male amebiasis patients had good results, compared to 33 per cent of the female. In general, one might conclude that about two thirds of the patients of both sexes had a satisfactory response to this medication regardless of the type of disease they had. Symptomatic relief of symptoms occurred in some patients after the first 2 or 3 doses. In others, it took a little longer, 2–3 days, before improvement was noticed. There appeared to be a decrease both in the number, frequency and severity of symptoms as the therapy was continued. Flatulence, distention, nausea, tightness in the abdomen, epigastric distress, or discomfort in the lower abdomen seemed to disappear in the order of frequency given. While the patients with irritable bowel had a more rapid improvement, satisfactory response was generally obtained in a higher percentage in those with duodenal ulcer. In patients with irritable bowel improvement in symptoms seemed to fluctuate at times. This was noted particularly in hospitalized patients.

The relief of symptoms—gas, fullness, nausea, pyrosis, epigastric discomfort, and so on—could be better evaluated in those patients who had no other medication; for example, the patients with irritable bowel. In a few instances the patients volunteered the information that this was the best "stomach-quieting medicine" they ever had, and 1 patient was almost angry at us for not having given her this medication earlier, instead of another antispasmodic and sedative which we had given her before.

Side Effects

There were only few side effects encountered in the hospital patients who used Donnatal. In a small number (10 per cent) of the outpatients the amount of the drug had to be decreased to half a tablet 3 times daily and at bedtime, because of a slight drowsiness which they experienced during the day on a dose of 1 whole tablet. Very few (8 per cent) complained of dryness of the mouth. One patient had visual disturbance on 1 tablet 4 times daily, which disappeared when the dose was cut in half. None of the side effects was severe enough to necessitate discontinuation of the tested substance. None of the patients developed constipation. It is noteworthy that Donnatal caused no urinary disturbances in this series of cases, while such complaints were encountered occasionally in patients taking other antispasmodics.

DISCUSSION

While it seems inadvisable to draw broad and unqualified conclusions concerning the efficacy of drugs based purely on clinical observations, we feel that some statements may be made concerning the clinical value of the substance which we tested, particularly since some of the results can be correlated with the findings in the secretory and motility studies. These observations suggest that in patients in whom there is a definite organic lesion like peptic ulcer or colitis, the therapeutic response can be more readily measured as to relief of pain than in the patients who have been grouped under the heading of irritable bowel. Whether a favorable result in patients with peptic ulcer depends on the decrease of acidity produced by these substances or by their effect on the motility is a moot question, because in this study the acidity was not remarkably reduced by the test substance, while the motility was decreased in only about two thirds of the cases. Nevertheless, one might conclude that, particularly in the patients who were grouped under irritable bowel, a relief of symptoms may have been due to the decrease in motility. In the patients with peptic ulcer a combination of decreased acidity and decreased motility may have accounted for the disappearance of symptoms.

From our observations it appears that a decrease in acidity does not run parallel with the decrease in motility, inasmuch as the test substance produced comparatively little decrease in the acidity but had good response in the motility study. From our motility studies we got the impression that the patients felt more comfortable at the time when the gastric motility was markedly decreased, and some patients complained of epigastric pain during the time when the gastric motility was markedly increased.

The fact that in the control cases no spontaneous disappearance of the gastric motility occurred during the observation period of over 3 hours makes us believe that the change (decrease) in motility observed following the test substance was due to the latter. Both the secretory and motility studies point to a definite latent period before the effect of the medication is felt, a fact which should be kept in mind by the clinician when he prescribes such substances. It is perhaps best to consider anywhere from 30 to 45 minutes as a latent period before the effect of the medication can be felt.

From our clinical observation and the results of the motility and secretory studies we are led to believe that this mixture of alkaloids

and sedatives is a useful one in the treatment of gastrointestinal conditions, whether they are on an organic or functional basis.

SUMMARY

1. An antispasmodic sedative mixture, Donnatal, was tested experimentally and clinically in a small group of patients for its effect on gastric secretion, gastric motility, and clinical symptoms.

2. The substance showed a mild antisecretory activity; that is, it reduced slightly the gastric acidity in the unstimulated stomach as compared with the secretion during the control day.

3. This substance produced a decrease in antral motility in over two thirds of the patients.

4. It gave symptomatic relief in about two thirds of the clinical cases tested.

5. This study does not permit any definite conclusion as to whether increased acidity or increased motility is the cause for ulcer pain, inasmuch as symptomatic relief was obtained in ulcer patients in whom little effect on the secretory curve and in others in whom little effect on the motility curve was noted.

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CLINICAL NOTES

MICROSCOPIC STOOL FINDINGS IN PARACOLOBACTRUM DIARRHEA

Oscar Felsenfeld, Lt. Col., M.C., USAR

IT IS common experience that typical stools resembling one or another of the textbook descriptions are uncommon in the respective types of diarrhea. The physician who would make his diagnosis only if he observed excrementa having the appearance of one or another of these "types" would certainly miss many a case. Perhaps a little more characteristic, but still far from diagnostic, are the microscopic pictures observed in dysenteric stools. Previous studies have shown, however, that even such studies have to be evaluated rather carefully,[3, 4, 6] since exceptions are numerous. Charcot-Leyden crystals, for instance, indicate an allergic response. They may be absent in amebic dysentery, and present in nonamebic conditions. Pus cells with pyknotic nuclei are often found in bacillary dysentery and will be seen also in the amebic type, especially when secondary infection intervenes. Macrophages are common in subchronic and chronic diarrhea of any origin. Molds and yeasts will be frequent especially in antibiotic-treated dysenteries. Erythrocytes appear whenever bleeding is present from ulcers, hemorrhoids, proctoscopic traumas, or other causes.

PARACOLOBACTRUM DIARRHEA

Paracolobactrum diarrhea (formerly called paracolon diarrhea) is usually a mild, acute disease which, as a rule, does not seriously affect adults. It appears both in outbreaks and in isolated instances. The causative organisms, or the strains which were isolated from such diarrheas, vary according to the geographic locality and way of living of the persons affected.[2] Several authors[1, 5] feel that *Paracolobactrum* should not be considered a separate genus but grouped if special common features are present (as the Arizona, Ballerup-Bethesda and Providence organisms), and those which are only slightly different from *Escherichia* and *Aerobacter-Klebsiella* should be classified with these latter genera. The reactions of the bowel as observed through

From the 406th Medical General Laboratory, APO 343, San Francisco, Calif.

microscopic stool examinations certainly do not differ from those observed in many other diarrheas. While the finding of the etiologic agent alone establishes the diagnosis of an infectious diarrhea, the presence of certain microscopic elements as pus, macrophages, Charcot-Leyden crystals, and so on, are indicative of the pathologic condition of the bowel and are of great importance in the evaluation of the course of the illness and the efficacy of therapeutic measures.

Thus the question to be answered is: Will microscopic examination help to differentiate *Paracolobactrum* diarrhea from other types, or should a warning be issued that in this diarrhea, as in the more familiar conditions like amebiasis, bacillary dysentery, and salmonellosis only the presence of the causative organism establishes the diagnosis of the disease?

MATERIAL AND FINDINGS

One hundred stools from acute and chronic *Paracolobactrum* diarrhea were studied to answer this question. They were sent from dispensaries in the Greater Tokyo area, preserved in 10% formalin. None of these 100 patients harbored *Salmonella*, *Shigella*, or any demonstrable pathogenic protozoa. The microscopic examination of these feces is summarized in Table 1.

DISCUSSION

These findings present a picture which cannot be considered diagnostic. Cellular elements pointing to acute or chronic inflammation, and to allergic response, were not uncommon. The relatively large proportion of stools which merited the comment "numerous molds and yeasts" may be due to antibiotic treatment. This comment was made on a subjective basis, usually if the elements comprised about one third of the material seen under the microscope. Whether mycologic

TABLE 1. Microscopic Findings in 100 Stools

	No. stools
Mucus	87
Pus	21
Macrophages	11
Charcot-Leyden crystals	8
Erythrocytes	7
Pyknotic bodies	8
Epithelial cells in clumps	6
Numerous molds and yeasts	22
Much undigested food	57
Fat globules	6

elements play a role in the course of *Paracolobactrum* diarrheas still has to be determined.

The same microscopic picture, however, is often seen in shigellosis and salmonellosis, especially during and after treatment. Thus it was not possible in the cases observed to discover features in the stools which would allow diagnosing *Paracolobactrum* diarrhea by microscopic stool examination.

SUMMARY

Microscopic studies of stools from patients with *Paracolobactrum* (paracolon) diarrhea did not reveal any characteristic features which would permit diagnosis without microbiologic studies.

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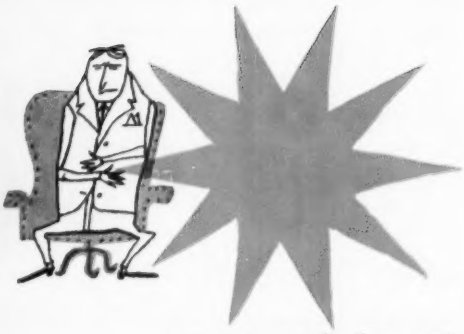

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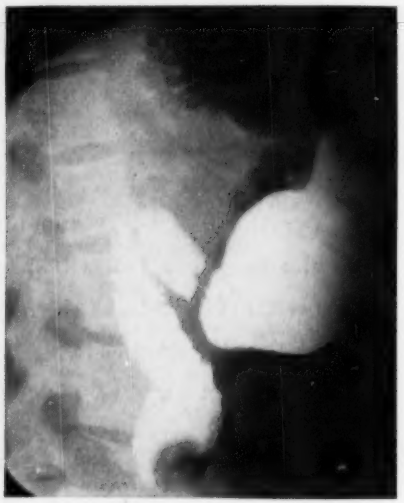

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*Roentgenograms and case history courtesy of I. Richard Schwartz, M.D., Kings County Gastrointestinal Clinic, Brooklyn, N. Y.

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